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RHINOLOGY

Endoscopic and clinical benefits of hyaluronic acid in children with chronic adenoiditis and middle ear disease

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Abstract Hyaluronic acid (HA) is involved in modulating inflammatory airway processes and mucociliary clearance. Some studies have tested the effectiveness of the topical administration of HA in patients with upper airway diseases with positive preliminary results. A prospective, single-blind, 1:1 randomised controlled study was performed to assess the efficacy and safety of the daily topical administration of 9 mg of sodium hyaluronate in 3 mL of a 0.9 % sodium saline solution on the basis of endoscopic and clinical parameters in children with chronic adenoiditis associated with recurrent acute otitis media and otitis media with effusion; age- and gender-matched children receiving normal 0.9 % sodium chloride saline solution were used as controls. Analysis was based on 103 (mean age 63.3 ± 18.2 months; 52 males, 50.5 %) children: 54 in the study group and 49 in the control group. A statistically significant reduction in the mean number of all acute otitis media episodes (AOME) (mean reduction 0.8 ± 0.4 per month; p value 0.05) and AOME without tympanic membrane perforation (mean reduction 0.6 ± 0.3 per month; p value 0.04) after recruitment was documented only in the study group. HA significantly improved all the endoscopic outcomes (p values ranging between 0.05 and <0.01) but one. Nasal washing with saline solution was effective on only three of them (p values ranging between 0.03 and <0.01). No untoward effects were documented. Our results confirm the safety and document the positive effect of topically administered HA solution on children with chronic adenoiditis associated with middle ear disease.

Keywords Recurrent acute otitis media · Adenoids · Hyaluronic acid · Children

Introduction

Hyaluronic acid (HA) is a high-molecular weight and ubiquitously endogenous glycosaminoglycan that acts as a component of many extra-cellular matrices found in respiratory epithelia, nasal and tracheobronchial mucosa, airway secretions, and gland serous cells [1]. It is a lubricant of airway surfaces, involved in the modulation of vascular tone and mucous gland secretion by acting on endothelin-1 [2], and thought to play a role in modulating inflammatory airway processes by regulating the migration and aggregation of polymorphonuclear leukocytes and monocytes [3]. The immunomodulation may be due to the balancing of the opposite effects of the low- and high-molecular weight fragments released during the inflammation-mediated breakdown of high-molecular weight HA: i.e., chemotaxis with trans-cellular signal activation, and immune suppression [4]. HA also regulates upper respiratory tract mucociliary clearance [5], as a result of the effect of the low- molecular weight, HA fragments released in the presence of the inflammatory molecules and free radicals that promote intra-cellular calcium accumulation and modulate the receptors for the HA-mediated motility responsible for increasing ciliary beat frequency [6].

Some studies have found that HA has in vitro anti-infective effects by promoting the phagocytosis of

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Streptococcus pyogenes [7, 8] and acting as an anti-adhesive and anti-biofilm molecule on Hep-2 cells exposed to bacterial species that are frequently isolated from patients with upper respiratory tract infection, as previously described [9]. Moreover, it has recently been suggested that HA may play central role in airway repair and remodelling to normal tissue function after traumatic events, including surgery [10].

On the basis of this, a few recent pilot studies have tested the effectiveness of the topical administration of HA in patients with upper airway diseases, such as allergic and non-allergic rhinitis, recurrent upper respiratory tract infections, and during recovery, after functional endoscopic sinus surgery, with positive preliminary results [5, 10–14]. In 2013, Macchi et al. [12] reported that treating 38 children affected by recurrent upper respiratory tract infections with nebulised HA nasal washes had beneficial effects on their clinical, endoscopic, and cytological outcomes, as it significantly reduced adenoidal hypertrophy (AH) and the presence of inflammatory cells in nasal mucosa, and improved the symptoms of rhinitis and nasal dyspnea.

The aim of this study was to assess the efficacy and safety of the topical nasal administration of an HA solution on the basis of endoscopic and clinical parameters in a selected case series of children with chronic adenoiditis associated with recurrent middle ear inflammation.

Methods

Study design and setting

This prospective, single-blind, randomised, and controlled trial was carried out at the University of Milan's Department of Clinical Sciences and Community Health between November 2014 and April 2015. The study is part of a larger project aimed at evaluating the safety and efficacy of the topical nasal administration of an HA-based compound in children with recurrent middle ear inflammation associated with chronic adenoiditis by assessing various clinical, instrumental, cytological, and microbiological outcomes.

The protocol was approved by our local ethics committee and the trial was conducted in accordance with the standards of Good Clinical Practice; written informed consent was obtained from the children's parents or legal guardians.

Study subjects

The study involved children aged 3–12 years affected by chronic adenoiditis associated with a history of recurrent acute otitis media (RAOM, defined as three episodes in the preceding 6 months and not more than four episodes in the preceding 12 months) [15] and otitis media with effusion (OME, defined as the presence for at least 3 months of middle ear effusion without any sign of concomitant acute middle ear inflammation, documented by means of pneumatic otoscopy and tympanometry) [16], who attended, in November 2014 through February 2015, the outpatient pediatric and otorhinolaryngology clinics for middle ear diseases. Chronic adenoiditis was defined as Cassano grade $\geq$3 AH assessed by means of flexible nasopharyngeal endoscopy [17] with ongoing nasopharyngeal inflammation or infection (at least three episodes of acute adenoiditis requiring antibiotic therapy in a period of 6 months or at least four episodes in a period of 12 months) [18].

The episodes of acute otitis media (AOM) were documented by means of the children's medical records, which had to include any combination of fever, earache, irritability, hyperemia or opacity accompanied by bulging of the tympanic membrane, or otorrhea. At least two episodes had to be supported by otoscopy and tympanometric findings.

The exclusion criteria were concomitant systemic diseases: craniofacial, neuromuscular, immunological, syndromic or defined genetic abnormalities; chronic eardrum perforation; previous ear surgery or adenoidectomy; neurosensory hearing loss; immunomodulatory treatment, vitamin D supplementation, or the use of complementary or alternative medications; acute febrile illness; and acute upper respiratory tract infection or antibiotic therapy in the previous 14 days.

Upon enrolment, a random number generator was used to randomise the patients 1:1 to:

- The control group, whose subjects received once daily administration of normal (0.9 % sodium chloride) saline solution (3 mL per nares) for 15 days a month for three consecutive months by means of a micronised nasal douche that nebulises particles with a median aerodynamic diameter of >10 micron (Rhinowash, Air Liquide Medical Systems Italy S.p.A., Brescia);
- The study group, whose subjects received once daily administration of 9 mg of sodium hyaluronate (Yabro, IBSA FARMACEUTICI ITALIA srl, Lodi) in 3 mL of a 0.9 % sodium saline solution (3 mL of solution per nares) for 15 days a month for three consecutive months using the same type of nasal douche (Rhinowash, Air Liquide Medical Systems Italy S.p.A., Brescia).

At the enrolment visit, a complete clinical history was taken, a record was made of each patients' gender, age, and allergy (documented by a positive skin prick test or radioallergosorbent tests and serum IgE levels within the

previous 12 months), and the most frequently encountered risk factors for AOM were assessed.

Upon enrolment and 3 months later, all of the children underwent a detailed otolaryngological examination, including nasal fiberoptic endoscopy, performed by two trained otolaryngologists who were blinded to the treatment received. The endoscopy was performed as previously described [19] using a 2.7 mm diameter endoscope without administering any local decongestants, anesthetic agents, or sedatives. The assessed features were the aspect and colour of the nasal mucosa, turbinate hypertrophy, the presence of anterior, nasopharyngeal or meatal secretions, or post-nasal drip, tubarian ostium patency, and the degree of AH scored on the basis of the criteria of Cassano et al. [17] as grade 1 = free choanal opening; grade 2 = adenoids occluding the upper half of the choanal opening without any tubarian ostium involvement; grade 3 = adenoids occluding 75 % of the choanal opening with partial tubarian ostium involvement; and grade 4 = adenoids completely occluding the choanal opening with an unevaluable tubarian ostium.

A record was also made of the number of AOM episodes with and without tympanic membrane perforation occurring in the 3 months before and after recruitment.

Statistical analysis

The sample size was determined on the basis of the primary endpoint of the main project (the impact of the topical administration of an HA solution on otoscopic and tympanometric signs of middle ear effusion) and computed considering the published data regarding the efficacy of tube insertion in reducing the prevalence of middle ear effusion in children with chronic OME [20, 21]. Assuming a standard deviation of 0.20, it was calculated that 58 subjects in each group would lead to a beta error margin of 0.20, an alpha value of 0.05, and a power of 80 %. Compliance with the assigned treatment was assessed by evaluating the number of returned phials.

The results are given as absolute numbers and percentages, or as arithmetical mean values ± standard deviation. The clinical and endoscopic outcomes were analysed using non-parametric tests.

The data were analysed using the STATA 10.0 software (StataCorp, College Station, Texas), and a p value of <0.05 was considered statistically significant.

Results

The final analysis was based on the findings relating to 103 (mean age 63.3 ± 18.2 months; 52 males, 50.5 %) of the 122 recruited children: 54 in the study group (mean age 63.7 ± 2.4 months; 28 males, 51.8 %) and 49 in the age- and gender-matched control group (mean age 62.9 ± 2.7 months; 24 males, 49.0 %) (Table 1). All of these patients successfully completed the treatment protocol as no returned vials were collected at the follow-up visits, and there were no untoward effects in either group (Fig. 1).

The mean number of AOM episodes documented in the 3 months before recruitment was 0.8 ± 1.3 per month, and the mean numbers of those with and without tympanic membrane perforation were, respectively, 0.5 ± 1.1 and 0.3 ± 0.6 episodes per month; about three-quarters of the children presented severe AH (Cassano grade 4) [17] (Table 1). Table 1 shows that the baseline demographic and clinical baseline characteristics of the two groups were comparable.

At the follow-up visit, there was a statistically significant reduction in the mean number of AOM episodes occurring after recruitment only in the study group (mean reduction 0.8 ± 0.4 per month; p value 0.05) (Table 2). The mean number of episodes without tympanic membrane perforation was significantly lower than at baseline in the study group (mean reduction 0.6 ± 0.3 per month; p value 0.04), but slightly, although not significantly higher than at baseline in the control group (mean increase 0.1 ± 0.1; p value n.s.). There was no significant difference in the mean number of episodes with tympanic membrane perforation before and after treatment in either group (Table 2).

In comparison with baseline, the topical administration of HA significantly improved all of the assessed endoscopic outcomes except the number of patients with nasal turbinate hypertrophy. It significantly reduced the prevalence of patients with severe AH (mean reduction 24.1 ± 8.7 %; p value <0.01), an obstructed Eustachian tube orifice (mean reduction 24.1 ± 8.7 %; p value <0.01), post-nasal drip (mean reduction 16.7 ± 5.5 %; p value <0.01), dyschromic and swollen nasal mucosa (mean reduction 40.3 ± 8.7 %; p value <0.01; and 20.4 ± 8.0 %; p value <0.01), moderate-severe turbinate hypertrophy (mean reduction 33.2 ± 9.7 %; p value <0.01), and nasopharyngeal, meatal, and anterior nasal secretions (mean reduction 13.6 ± 8.5 %; p value 0.05; 7.5 ± 3.6 %; p value 0.02; and 24.1 ± 8.0 %; p value <0.01) (Table 3).

Nasal washing with saline solution was effective on only three of the ten endoscopic parameters: the prevalence of patients with: anterior nasal secretions (mean reduction 16.3 ± 8.8 %; p value 0.03), dyschromic nasal mucosa (mean reduction 40.8 ± 9.2 %; p value <0.01), and moderate-to-severe turbinate hypertrophy (mean reduction 25.5 ± 1.0 %; p value <0.01) (Table 3).

Table 1 Demographic and clinical characteristics of the study population at baseline

Characteristics	Total (103 pts.)	Control group (49 pts.)	Study group (54 pts.)	*p* value
Mean age ± SD, months	63.3 ± 18.2	62.9 ± 2.7	63.7 ± 2.4	n.s.
Males (%)	52 (50.5)	24 (49.0)	28 (51.8)	n.s.
Diagnosis				
OME	50 (48.5)	23 (47.0)	27 (50.0)	n.s.
RAOM	29 (28.2)	15 (30.6)	14 (25.9)	n.s.
OME + RAOM	24 (22.3)	11 (22.4)	13 (24.1)	n.s.
Family history of AOM	44 (22.7)	23 (47.0)	21 (38.9)	n.s.
Family history of deafness	3 (2.9)	1 (2.0)	2 (3.7)	n.s.
Family history of allergy	58 (56.3)	32 (65.3)	26 (48.1)	n.s.
No. of pts. with siblings	45 (43.7)	22 (44.9)	23 (42.6)	n.s.
Mean No. of siblings ± SD	0.5 ± 0.7	0.5 ± 0.1	0.5 ± 0.1	n.s.
Prematurity	7 (6.8)	4 (8.2)	3 (6.6)	n.s.
Neonatal problems	11 (10.7)	6 (12.2)	5 (9.3)	n.s.
Breastfeeding	66 (64.1)	31 (63.3)	35 (64.8)	n.s.
Allergy (%)	21 (20.4)	9 (18.4)	12 (22.2)	n.s.
Daycare attendance (%)	103 (100)	49 (100)	54 (100)	n.s.
Pacifier use	2 (2.0)	2 (4.1)	0 (0.0)	n.s.
Second-hand smoke exposure	36 (34.9)	17 (34.7)	19 (35.2)	n.s.
Influenza immunization (%)	23 (22.2)	10 (20.4)	13 (24.1)	n.s.
PVC7 immunization	87 (84.5)	40 (81.6)	47 (87.0)	n.s.
Nasal washing				
No	2 (2.0)	1 (2.0)	1 (1.9)	n.s.
Sporadic	6 (5.8)	2 (4.1)	4 (7.4)	n.s.
Daily	95 (92.2)	46 (93.9)	49 (90.7)	n.s.
Mean No. of episodes of AOM without perforation*	0.5 ± 1.1	0.2 ± 0.1	0.8 ± 0.3	n.s.
Mean No. of episodes AOM with perforation*	0.3 ± 0.6	0.3 ± 0.2	0.3 ± 0.2	n.s.
Mean No. of episodes of AOM*	0.8 ± 1.3	0.5 ± 0.2	1.1 ± 0.4	n.s.
Adenoidal hypertrophy grade**				
3	24 (23.3)	13 (26.5)	11 (20.4)	n.s.
4	79 (76.7)	36 (73.5)	43 (79.6)	n.s.

No. number, *pts.* patients, *SD* standard deviation, *n.s.* not significant, *OME* otitis media with effusion, *RAOM* recurrent acute otitis media, *AOM* acute otitis media, *PVC7* pneumococcal conjugate vaccine

* Per month, in the previous 3 months

** Cassano's classification [17]

Discussion

This is the first randomised, controlled clinical trial to evaluate the effects of a topically administered HA solution on the exacerbations of AOM and its related nasopharyngeal endoscopic parameters in a selected population of children with chronic adenoiditis associated with a history of RAOM and OME.

At the end of the treatment period, the children in the experimental group experienced significantly fewer AOM episodes than at baseline, with a mean global reduction of 0.8 ± 0.4 episodes and a mean reduction of 0.6 ± 0.3 episodes without perforation, whereas there was no significant difference in the control group. To the best of our knowledge, the most similar previously published study is that of Macchi et al. [12], who enrolled a sample of children with recurrent upper airway tract infections (including rhinitis, rhinosinusitis, adenoiditis, pharyngitis, otitis media, tubotympanitis, and tonsillitis), but did not evaluate the number of acute infectious episodes. The efficacy of HA treatment has been previously reported in patients with lower airway disease [22, 23], and is thought to be due to on a stimulatory effect on host cellular defence mechanisms [22], including enhanced neutrophil functions, and on the regulation of bronchial hyperactivity and remodelling in predisposed patients [23]. Subcutaneous HA administration has also been previously tested in a small sample of patients with recurrent exacerbations of chronic

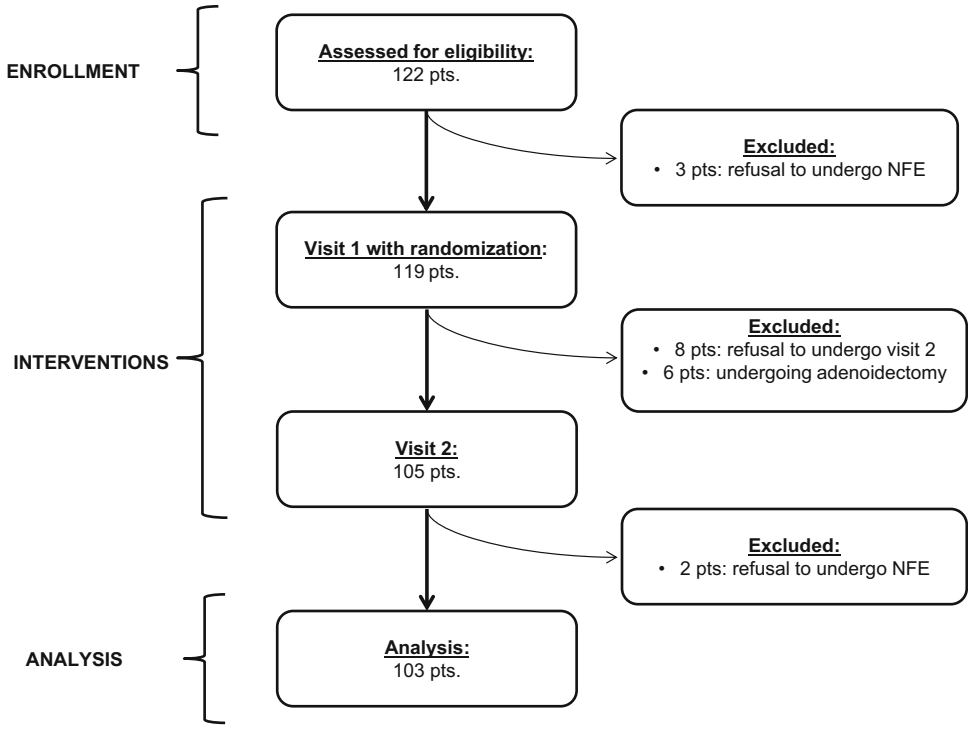

Fig. 1 Study flow chart

Table 2 Mean number of acute otitis media episodes (per month, in the previous 3 months) ± standard deviation before and after treatment

Group	AOM episodes without perforation		AOM episodes with perforation		Total AOM episodes	
	Control	Study	Control	Study	Control	Study
Pre-treatment	0.2 ± 0.1	0.8 ± 0.3	0.3 ± 0.2	0.3 ± 0.2	0.5 ± 0.2	1.1 ± 0.4
Post-treatment	0.3 ± 0.2	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.4 ± 0.2	0.4 ± 0.2
Reduction ± SD	−0.1 ± 0.1	0.6 ± 0.3	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.2	0.8 ± 0.4
p value	n.s.	0.04	n.s.	n.s.	n.s.	0.05

n.s. not significant, *AOM* acute otitis media

bronchitis, in whom it reduced the recurrence of acute infections and antibiotic consumption in comparison with placebo [23].

Jang et al. [24] postulated a protective effect of HA on middle ear mucosa in an animal study that evaluated the anti-inflammatory and anti-adhesive effects of antibiotic/steroid packing containing soluble HA-carboxymethyl cellulose placed in the middle ear of guinea pigs with experimentally induced *Pseudomonas aeruginosa* lipopolysaccharide otitis media after having abraded the middle ear mucosa. The results obtained were better than those observed in the controls in terms of middle ear aeration, mucosal thickening, and improved auditory brainstem responses.

Our findings documented a significant improvement from baseline in all of the assessed endoscopic parameters, except for the prevalence of patients with turbinate hypertrophy, in the treatment group, whereas the children in the control group showed a significant improvement only in terms of the presence of anterior nasal secretions, dyschromic nasal mucosa, and moderate-severe turbinate hypertrophy. The partial improvement in the control group can be explained by the fact that nasal washing with 0.9 % saline solution cannot be considered a placebo treatment, but an inexpensive and safe means of reducing nasal secretion that is widely used prophylactically and therapeutically in children with upper respiratory tract conditions in everyday clinical practice [25, 26].

It is worth noting that topically administered HA solution not only significantly reduced the presence of secretions (nasopharyngeal, meatal and anterior nasal secretions, and post-nasal drip), but also reduced the presence of dyschromic or swollen nasal mucosa, and moderate-severe hypertrophy of the nasal turbinates, and had a positive effect on the degree of adenoidal hypertrophy and Eustachian tube ostial patency. The prevalence of children with severe adenoidal hypertrophy (i.e., Cassano grade 4) [17] or an obstructed Eustachian tube ostium, respectively,

Table 3 Endoscopic outcomes before and after treatment in control and study groups

Group	No. of pts. with grade 4 AH (%)		No. of pts. with NP secretions (%)		No. of pts. with meatal secretions (%)		No. of pts. with obstructed ET ostium (%)	
	Control	Study	Control	Study	Control	Study	Control	Study
Pre-treatment	36 (73.5)	43 (79.6)	15 (30.6)	18 (34.0)	5 (10.2)	4 (5.5)	47 (83.7)	47 (87.0)
Post-treatment	30 (61.2)	30 (55.5)	13 (26.5)	11 (20.4)	2 (4.1)	0 (0.0)	38 (77.5)	36 (66.7)
Difference ± SD	12.2 ± 9.4	24.1 ± 8.7	4.1 ± 9.1	13.6 ± 8.5	6.1 ± 5.2	7.5 ± 3.6	6.3 ± 8.5	20.4 ± 7.9
p value	n.s.	<0.01	n.s.	0.05	n.s.	0.02	n.s.	<0.01
Group	No. of pts. with post-nasal drip (%)		No. of pts. with anterior nasal secretions (%)		No. of pts. with dyscromic nasal mucosa (%)		No. of pts. with swollen nasal mucosa (%)	
	Control	Study	Control	Study	Control	Study	Control	Study
Pre-treatment	3 (6.1)	10 (18.5)	17 (34.7)	20 (37.0)	33 (67.3)	34 (63.0)	38 (77.5)	42 (77.8)
Post-treatment	6 (12.2)	1 (1.8)	9 (18.4)	7 (13.0)	13 (26.5)	12 (22.6)	30 (61.2)	31 (57.4)
Difference ± SD	+6.1 ± 5.8	16.7 ± 5.5	16.3 ± 8.8	24.1 ± 8.0	40.8 ± 9.2	43.3 ± 8.7	16.3 ± 5.3	20.4 ± 8.0
p value	n.s.	<0.01	0.03	<0.01	<0.01	<0.01	n.s.	<0.01

Group	No. of pts. with turbinate hypertrophy (%)		No. of pts. with moderate-severe turbinate hypertrophy (%)	
	Control	Study	Control	Study
Pre-treatment	42 (85.7)	44 (81.5)	23 (54.8)	23 (52.3)
Post-treatment	41 (83.7)	42 (77.8)	12 (29.3)	8 (19.0)
Difference ± SD	2.0 ± 7.3	3.7 ± 7.7	25.5 ± 1.0	33.2 ± 9.7
p value	n.s.	n.s.	<0.01	<0.01

No. number, *pts.* patients, *n.s.* not significant, *AH* adenoidal hypertrophy, Cassano's classification [17], *NP* nasopharyngeal, *ET* Eustachian tube

decreased from about 80–55 %, and from about 87–67 %. This global improvement in nasal patency partially accounts for the positive effect of HA on the number of AOM episodes, given the strict anatomic and functional relationship between the nasopharyngeal/adenoidal sites and the tubotympanic unit, as well as the well-known etiological role of chronic nasopharyngeal infections in the development of recurrent middle ear inflammation [18].

Our findings are consistent with those of the previous studies of the topical administration of an HA solution in various small patient series [5, 10–14]. Gelardi et al. documented a reduction in the presence of rhinorrhea and endoscopically detectable secretions in 39 patients with allergic or non-allergic rhinitis [13], and in 19 patients after functional endoscopic sinus surgery [5]. Macchi et al. [12] found that twice daily treatment with HA 9 mg on 15 days per month for 3 months was associated with a significant improvement in AH, as shown by univariate and multivariate regression analyses of children with recurrent upper respiratory tract infections. In addition, Gelardi et al. [13] reported an albeit non-significant positive trend towards an improvement in nasal mucosa edema and hyperemia in patients with rhinitis, and the same was found by Macchi et al. [12] in children with recurrent upper respiratory tract infections. On the contrary, the improvement in post-nasal drip observed by us has not been previously described.

The significant reduction in the mean number of total and uncomplicated AOM episodes after topical HA administration may have been due to the positive effect of HA on upper airway mucociliary clearance, its immunoregulatory effects, and its anti-infective action [2–5]. It has recently been suggested that it may have anti-biofilm effect as it inhibits the in vitro adhesion of respiratory pathogens to epithelial surface in a concentration-dependent manner and also has moderate inhibitory activity against biofilm formation [9]. The clinical impact of HA on the biofilms involved in upper airway disease has been previously evaluated by means of nasal cytology with conflicting results: Macchi et al. [12] reported a significant mean 42 % reduction in the prevalence of children with upper respiratory tract infection after HA administration, but Gelardi et al. [13] found no significant changes in patients with allergic or non-allergic rhinitis. On the basis of these findings, we are planning to use microbiological techniques to assess the possible effect of our treatment protocol on the formation and the presence of biofilm in children with chronic adenoiditis associated with recurrent middle ear inflammation as part of our larger project.

Conclusion

Our results confirm the safety and document of the globally positive effect of topically administered HA solution on children with chronic adenoiditis associated with a history of RAOM and OME, and suggest that our treatment protocol can be considered as complementary to the traditional therapies for prevention and treatment in such patients. Further studies on selected samples are welcome to confirm these preliminary results.

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Compliance with ethical standards

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Conflict of interest Authors do not have any financial relationship with the organization that sponsored the study.

References

1. Baraniuk JN, Shizari T, Sabol M et al (1996) Hyaluronan is exocytosed from serous, but not mucous cells, of human nasal and tracheobronchial submucosal glands. J Investig Med 44:47–52
2. Mullol J, Chowdhury BA, White MV et al (1993) Endothelin in human nasal mucosa. Am J Resp Cell Mol Biol 8:393–402
3. Partsch G, Schwarzer C, Neumüller J et al (1989) Modulation of the migration and chemotaxis of PMN cells by hyaluronic acid. Z Rheumatol 8:123–128
4. Krasinski R, Tchorzewski H (2007) Hyaluronan-mediated regulation of inflammation. Postepy Hig Med Dosw 61:683–689 **(online)**
5. Gelardi M, Guglielmi AV, De Candia N et al (2013) Effect of sodium hyaluronate on mucociliary clearance after functional endoscopic sinus surgery. Eur Ann Allergy Clin Immunol 45:103–108
6. Manzanares D, Monzon ME, Savani RC et al (2007) Apical oxidative hyaluronan degradation stimulates airway ciliary beating via RHAMM and RON. Am J Resp Cell Mol Biol 37:160–168
7. Kawabata S, Kuwata H, Nakagawa I et al (1999) Capsular hyaluronic acid of group A streptococci hampers their invasion into human pharyngeal epithelial cells. Microb Pathog 27:71–80
8. Cywes C, Stamenkovic I, Wessels MR (2000) CD44 as a receptor for colonization of the pharynx by group A *Streptococcus*. J Clin Invest 106:995–1002
9. Drago L, Cappelletti L, De Vecchi E et al (2014) Antiadhesive and antibiofilm activity of hyaluronic acid against bacteria responsible for respiratory tract infections. Acta Pathol Microbiol Immunol 122:1013–1019
10. Castelnuovo P, Tajana G, Terranova P et al (2015) From modeling to remodeling of upper airways: centrality of hyaluronan (hyaluronic acid). Int J Immunopathol Pharmacol 21:160–167
11. Macchi A, Terranova P, Digilio E et al (2013) Hyaluronan plus saline nasal washes in the treatment of rhino-sinusal symptoms in patients undergoing functional endoscopic sinus surgery for rhino-sinusal remodeling. Int J Immunopathol Pharmacol 26:137–145
12. Macchi A, Castelnuovo P, Terranova P et al (2013) Effects of sodium hyaluronate in children with recurrent upper respiratory tract infections: results of a randomised controlled study. Int Immunopathol Pharmacol 26:127–135
13. Gelardi M, Iannuzzi L, Quaranta N (2013) Intranasal sodium hyaluronate on the nasal cytology of patients with allergic and nonallergic rhinitis. Int Forum Allergy Rhinol 3:807–813
14. Varricchio A, Capasso M, Avvisati F et al (2014) Inhaled hyaluronic acid as ancillary treatment in children with bacterial acute rhinopharyngitis. J Biol Regul Homeost Agents 28:537–543
15. Gates GA, Klein JO, Lim DJ et al (2002) Recent advances in otitis media. 1. Definitions, terminology, and classification of otitis media. Ann Otol Rhinol Laryngol Supp 188:8–18
16. American Academy of Family Physicians, American Academy of Otolaryngology—Head and Neck Surgery and American Academy of Pediatrics Subcommittee on Otitis Media With Effusion (2004) Otitis media with effusion. Pediatrics 113:1412–1429
17. Cassano P, Gelardi M, Cassano M et al (2003) Adenoid tissue rhinopharyngeal obstruction grading based on fiberendoscopic findings: a novel approach to therapeutic management. Int J Pediatr Otorhinolaryngol 67:1303–1309
18. Marseglia GL, Poddighe D, Caimmi D et al (2009) Role of adenoids and adenoiditis in children with allergy and otitis media. Curr Allergy Asthma Rep 9:460–464
19. Torretta S, Marchisio P, Cappadona M et al (2013) Nasopharyngeal fiberendoscopy in children: a diagnostic challenge in current clinical practice: how we do it. Int J Pediatr Otorhinolaryngol 77:747–751
20. Browning GG, Rovers MM, Williamson I et al (2010) Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane Database Syst Rev 6:CD001801
21. Rovers MM, Black N, Browning GG et al (2005) Grommets in otitis media with effusion: an individual patient data meta-analysis. Arch Dis Child 90:480–485
22. Petrigni G, Allegra L (2006) Aerosolised hyaluronic acid prevents exercise-induced bronchoconstriction, suggesting novel hypotheses on the correction of matrix defects in asthma. Pulm Pharmacol Ther 19:166–171
23. Venge P, Pedersen B, Håkansson L et al (1996) Subcutaneous administration of hyaluronan reduces the number of infectious exacerbations in patients with chronic bronchitis. Am J Respir Crit Care Med 153:312–316
24. Jang CH, Cho YB, Choi CH et al (2013) Effect of anti-adhesion barrier solution containing ciprofloxacin-hydrocortisone on abraded mucosa with otitis media. Int J Pediatr Otorhinolaryngol 77:19–24
25. Marchisio P, Picca M, Torretta S et al (2014) Nasal saline irrigation in preschool children: a survey of attitudes and prescribing habits of primary care pediatricians working in northern Italy. Ital J Pediatr 5:47
26. Marchisio P, Varricchio A, Baggi E et al (2012) Hypertonic saline is more effective than normal saline in seasonal allergic rhinitis in children. Int J Immunopathol Pharmacol 25:721–730